compare changes in lower limb muscle force production and hip joint contact forces (JCF) during a 30-minute walking task between people with and without HOA.

Methods: Ten asymptomatic, healthy controls without radiographic HOA (Kellgren-Lawrence [KL] < 2) and no signs of hip cartilage damage measured via MRI and 18 individuals with radiographic HOA (KL 2 – 3) were recruited for this study. All participants completed the Hip disability and Osteoarthritis Outcome Score (HOOS) to assess self-reported hip pain. Controls were considered asymptomatic if they reported a HOOS pain score > 80. All study participants underwent 3D motion analysis using 14 cameras and an instrumented split belt treadmill while performing a 30-minute walking task at a self-selected speed. Self-reported hip pain was obtained at the start (T0) and end (T30) of the walking task for all participants using a visual analog scale (0–10). OpenSim was used to create subject-specific musculoskeletal simulations for each participant in order to quantify lower limb muscle force production and hip JCF during the walking task. All muscle forces and hip JCF parameters were normalized by bodyweight (BW). Between group differences in age, HOOS pain sub-scores and changes in self-reported hip pain during the walking task (T30 – T0) were compared using Mann-Whitney U-tests while between-group differences in BMI and gait speed were compared using independent t-tests. Sex distribution between the groups was compared using a Fisher's Exact Test. A repeated measures ANCOVA, adjusting for gait speed, was used to compare within- and between-group differences in peak muscle forces and hip JCF at the T0 and T30 time points.

Results: Age, BMI and sex distribution were similar between groups (Table 1). The HOA group reported significantly lower HOOS pain scores (worse hip pain) and walked slower than the controls. Groups exhibited similar changes in self-reported hip pain (Δ VAS p=0.16) during the walking task. Between-group effects indicated that HOA ambulated with significantly lower peak piriformis, lower sartorius and higher peak quadriceps muscle forces as well as a trend of higher peak gluteus medius muscle forces throughout the 30-minute walking task. We also observed an interaction effect (time*group) whereby HOA exhibited lower peak sartorius muscle force at T30 compared to the controls. There were no within- or between-group differences in hip JCF during the walking task.

Conclusions: The purpose of this study was to assess potential changes in lower limb neuromuscular patterns and hip JCF during a 30-minute walking task (aerobic exercise) in individuals with and without HOA. The HOA group exhibited lower HOOS pain scores (worse hip pain) and slower gait speeds. Despite similar changes in hip pain and hip JCF as the controls, the HOA group ambulated with lower hip flexor muscle forces as well as higher hip abductor and knee extensor muscle forces throughout the 30-minute walking task. The lower peak piriformis and sartorius muscle forces (hip flexors) in the HOA group may place a larger demand on the gluteus medius (hip abductor) to assist with pelvic stabilization and may explain the overall higher gluteus medius muscle force in the HOA group. The higher peak quadriceps force (knee extensors) may suggest that the HOA group is utilizing distal joint musculature to provide additional lower limb stabilization during the prolonged walking task. The slower gait speed and these altered hip and knee neuromuscular patterns in the HOA group may be compensatory mechanisms to reduce hip pain during prolonged walking (aerobic exercise). Future studies should investigate potential alterations in muscle activation that may help to explain these altered hip and knee muscle force patterns during aerobic exercise and would help to develop targeted rehabilitation interventions for HOA. The similar hip JCF and pain levels support prolonged walking as a reasonable aerobic exercise option for individuals with HOA.

Table 1: Group Demographics and Biomechanical Outcomes at the Start (T0) and end (T30) of the 30-Minute Walking Task, Reported as Gait-Speed Adjusted Mean±Standard Error

	Healthy Controls (N=10)		HOA (N=18)		p-values	
Age (years)	54.6±8.55		59.9±9.39		0.15	
Sex (M:F)	3:7		8:10		0.69	
BMI (kg·m^{-2})	27.0±2.81		25.3±3.26		0.16	
HOOS Pain	96.0±6.89		73.6±20.1		< 0.01	
Gait Speed (m·s^{-1})	0.97±0.14		0.79±0.23		0.03	
Δ VAS Hip Pain	-0.1±0.31		0.94±1.73		0.16	
Muscle and JCF Forces Reported in Bodyweights	T0	T30	T0	T30	Between Group Effect	Interaction Effect
Piriformis	0.06±0.01	0.05±0.18	0.09±0.01	0.11±0.01	0.04	0.14
Sartorius	0.10±0.02	0.14±0.01	0.08±0.01	0.07±0.01	0.01	0.02
Quadriceps	0.51±0.13	0.54±0.13	0.88±0.09	0.97±0.10	0.02	0.39
Gluteus Medius	0.95±0.08	1.01±0.09	1.16±0.06	1.22±0.06	0.06	0.98
Anterior JCF	1.14±0.17	1.11±0.17	1.30±0.12	1.27±0.12	0.45	0.95
Posterior JCF	0.13±0.03	0.14±0.03	0.10±0.02	0.09±0.24	0.37	0.36
Superior JCF	4.31±0.37	4.21±0.37	4.52±0.27	4.34±0.27	0.71	0.72
Medial JCF	1.04±0.08	1.02±0.09	1.11±0.05	1.10±0.06	0.43	0.92
JCF Magnitude at P1	4.50±0.41	4.24±0.42	4.64±0.30	4.35±0.30	0.82	0.93
JCF Magnitude at P2	4.20±0.37	4.21±0.33	4.10±0.27	3.97±0.24	0.70	0.46

P1: Peak during loading response; P2: Peak during terminal stance

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EVALUATION OF EFFICACY AND SAFETY OF A FIXED-DOSE COMBINATION OF APOCYNIN AND PAEONOL IN KNEE OA PATIENTS WITH MODERATE TO SEVERE PAIN AND NOCIPLASTIC PAIN FEATURES: A PHASE 2B TRIAL

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Purpose (the aim of the study) Purpose: Current treatments for OA are limited to symptoms and associated with poor efficacy or serious safety risks. So there is a great unmet need for new OA therapies.

A fixed-dose combination of apocynin and paeonol in a ratio of 2:7 (APPA) has been shown to inhibit activation of the Nuclear-Factor Kappa-B (NF-κB) cascade, upregulate Nrf2, and to have senolytic effects, all relevant OA targets. APPA was previously evaluated in a Phase 2a trial, where it was associated with positive signals of efficacy in OA patients with possible nociplastic pain features and moderate to severe pain, but the trial was limited by short duration of treatment, and the trial evaluated only a single APPA dose regimen.

This report describes the results of the subsequent phase 2b trial evaluating 12 weeks of treatment with APPA in two dose regimens versus placebo, in people with knee OA, with moderate to severe pain and nociplastic features.

Methods: The trial was a randomized, double-blind, placebo-controlled trial where a total of 225 participants were randomized 1:1:1 between oral APPA 800 or 1200 mg, or placebo twice daily and treated for 12 weeks.

The main inclusion criteria were radiographic knee OA with a KL-grade 2 or 3, a WOMAC pain score ≥50 and ≤90 out of 100 of the target knee, and a PainDETECT score of ≥13 out of 38. The main exclusion criteria included recent intraarticular interventions, hip pain greater than the target knee, and BMI ≥40 kg/m2. The primary endpoint was change from baseline to Day 84 in the WOMAC pain score. Key secondary endpoints included Weekly Average of Daily Pain, ICOAP, other WOMAC domains, Patient Global Assessment, OMERACT-OARSI Responder criteria and EQ-5D. Safety outcomes included adverse events (AE), lab parameters, ECG, and vital signs.

Pharmacokinetics (PK) were assessed in a substudy involving 24 patients, and population PK was assessed in all participants.

Pre-planned subgroup analyses included participants with higher baseline pain scores.

The efficacy analyses were performed in the mITT population and relevant subgroups. The treatment effect on continuous variables was assessed by an MMRM, including relevant covariates, and binary outcomes by a logistical regression model. For the primary endpoint, the statistical testing was conducted in a hierarchical manner. No adjustment for multiplicity was performed for other endpoints.

Results: A total of 225 participants were randomized, of which 205 (91.1 %) completed the trial. The mean age was 63.9 (SD: 8.0), years, a mean BMI of 28.2 kg/m^2 (SD: 4.4), baseline target knee WOMAC pain was 32.2 out of 50 (SD: 4.7), the mean PainDETECT score was 17.6 (SD: 3.5) out of 38, and 57.6% of the population were females.

The main efficacy outcomes are illustrated in Figure 1.

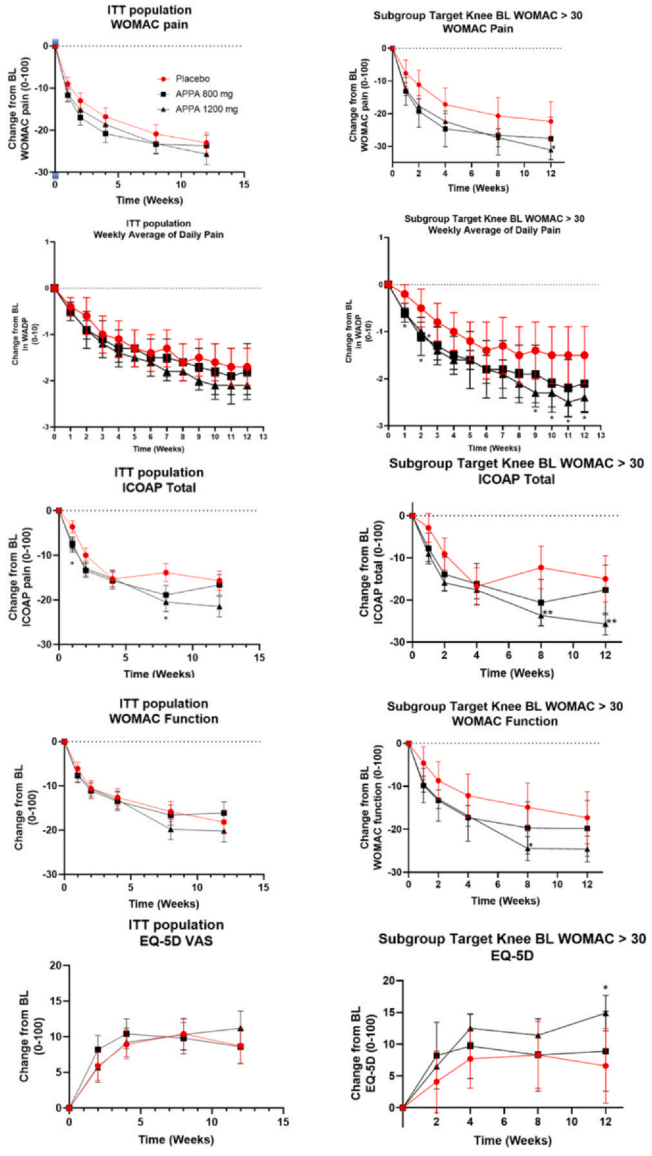
For the primary endpoint, there was no statistically significant difference in the change from baseline to Week 12 on WOMAC pain between APPA and placebo. Among the secondary endpoints, a consistent signal indicating a dose-dependent beneficial effect of APPA was observed in Weekly average of Daily Pain and ICOAP.

In the pre-planned subgroup analysis of participants with higher WOMAC pain at baseline, a consistent, dose-dependent, and in the highest APPA dose group, for several outcomes, statistically significant benefit was observed, including WOMAC pain, function and total, ICOAP, WADP, EQ-5D, and OMERACT-OARSI responders.

The safety and tolerability of APPA was generally very good. The most frequently reported AEs were (placebo/APPA 800/APPA1200): GI reflux (1.3 %/ 8.3 %/8.0 %), dyspepsia (3.9 %/8.3 %/4.0 %) and diarrhoea (5.2%/ 1.4%/6.7%), all reported as mild. Vital signs, ECG parameters, serum chemistry and hematology were stable throughout the trial.

Preliminary assessments of PK indicated variability in the absorption of APPA (data not shown), the influence of which, if any, on PD is being evaluated.

Conclusions: In this phase 2b trial, APPA was not associated with a significant improvement in WOMAC pain compared to placebo, however signals of efficacy were observed in other efficacy endpoints. Subgroup analyses of participants with higher baseline pain suggest clinically relevant efficacy of APPA 1200 mg in this population, warranting further research. APPA was well tolerated and safe.



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PREVALENCE AND DEVELOPMENT OF ACETABULAR DYSPLASIA FROM CHILDHOOD TO ADULTHOOD: IMPLICATIONS FOR HIP OSTEOARTHRITIS PREVENTION

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Purpose (the aim of the study): Acetabular dysplasia (AD) is an important risk factor for hip osteoarthritis, particularly in younger individuals. While diagnostic and treatment efforts focus on developmental hip dysplasia in infants (incidence 1-3%), AD prevalence in adults (5-21%) suggests missed diagnoses, insufficient treatment, and/or later development. Understanding AD development is crucial for preventing joint degeneration. More knowledge of the prevalence of AD in the general population is required to understand its development during growth. This study aimed to 1) estimate AD prevalence in 18-year-olds from the general population, 2) compare different AD definitions, and 3) investigate prevalence changes from age 9 to 18 years.

Methods: We used data from The Generation R Study, a prospective, population-based cohort. For cross-sectional analysis, 3,046 18-year-olds with right hip DXA images were included. Longitudinal analysis involved 347 participants with DXAs at ages 9, 13, and 18. AD was defined using Wiberg center edge angle (WCEA) ≤ 20°, acetabular depth-width ratio (ADR) ≤ 250, and modified acetabular index (mAI) ≥ 13° at age 18. The lateral center edge angle (LCEA) was used instead of the WCEA at ages 9 and 13 years, with AD defined as an LCEA ≤ 20° at age 13 years and an LCEA ≤ 15° at age 9 years to account for the developing acetabulum. Additionally, at age 9, an acetabular index (AI) ≥ 18° was used instead of the mAI. A composite definition classified hips as dysplastic if at least one criterion indicated dysplastic. Hip morphology was measured automatically using validated in-house developed methods. While hip morphology traditionally is measured on radiographs, there is good reliability and agreement between DXA images and pelvic radiographs. Prevalence was estimated with 95% CI using the Wilson score interval; overlap and changes were visualized using Venn and Alluvial diagrams, respectively.

Results: The main analysis (n=3,046, mean age 18.4 ± 0.7 years, 56% female) found an AD prevalence of 6.6% (95% CI, 5.7%-7.5%) using WCEA, while the composite definition yielded 20.3% (95% CI, 18.9%-21.7%). The overlap in AD definitions is visualized in Figure 1. The ADR was the largest contributor to the composite prevalence.

The longitudinal analysis (n=347, 56% female) showed a composite prevalence of 17.3% (95% CI, 13.7%-21.6%) at age 9, 9.2% (95% CI, 6.6%-12.7%) at age 13, and 17.9% (95% CI, 14.2%-22.2%) at age 18. The change in composite prevalence over time has been visualized in Figure 2. Of participants with AD at age 18, 48% developed it only by age 18, and 24% had AD at all three timepoints.

Conclusions: The ADR classified the most hips as dysplastic in 18-year-olds, with 67 of the 617 composite AD cases meeting all three definitions. The clinical relevance of these composite classified dysplastic hips needs to be determined. AD prevalence highly depends on the definition used and thus can change over time, with only 24% of 18-year-olds with AD consistently having AD at ages 9, 13, and 18. This is an initial insight into AD development during growth. A better understanding of AD development during growth is crucial, as this knowledge can inform prevention strategies for AD, and consequently, mitigate the risk of OA in younger individuals.

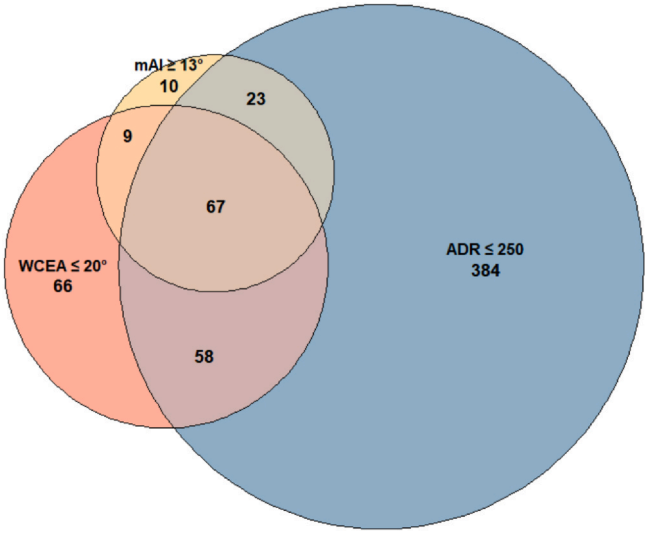


Figure 1: Venn diagram of the three definitions of acetabular dysplasia. mAI: modified acetabular index. WCEA: Wiberg center edge angle. ADR: acetabular depth-width ratio.